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MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PETER AADAL,
GUNNAR ANDERSSON, and OLGA ANDERSSON

Appeal 2016-002719
Application 13/387,094
Technology Center 1600

Before JEFFREY N. FREDMAN, ROBERT A. POLLOCK, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to a method for determining whether a nanoparticle is transported across the blood-brain barrier. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"The present invention is directed to insect models that are aimed to reflect vertebrate blood-brain barrier (BBB) penetration of nanoparticles.

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[1] Appellants identify the Real Party in Interest as N2MO A/S (*see* App. Br. 2).

Investigation of BBB penetration of nanoparticles is extremely important since there is an increasing use of nanoparticles and the profile for many of these are yet to be understood" (Spec. 1:7–10). "On the one hand successful CNS drugs have to cross the BBB. On the other hand BBB penetration of nanoparticles may also cause unwanted side effects" (Spec. 1:12–13).

The Claims

Claims 1, 3–7, and 9–12 are on appeal. Claim 1, the sole independent claim, is representative and reads as follows:

> 1. A method for determining whether a nanoparticle is transported across the blood brain barrier (BBB), said method comprises the steps of:
>
> administering the nanoparticle to an insect having a BBB, wherein the insect is selected from the group consisting of the orders Blattoidea and Acridoidea;
>
> incubating the insect;
>
> dissecting the brain from the insect; and
>
> measuring the concentration of the nanoparticle in the brain.

The issue

The Examiner rejected claims 1, 3–7, and 9–12 under 35 U.S.C. § 103(a) as obvious over Thomas,[2] Poss,[3] Labhesetwar,[4] Stork,[5] and Mayer[6] (Ans. 2–7).

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[2] Thomas, M., *Insect Blood-Brain Barrier: A Radioisotope Study of the Kinetics of Exchange of a Liposoluble Molecule (n-Butanol)*, 64 J. Exp. Biol. 119–130 (1976) ("Thomas").
[3] Poss et al., US 2005/0214221 A1, published Sept. 29, 2005 ("Poss").
[4] Labhasetwar et al., US 7,332,159 B2, issued Feb. 19, 2008 ("Labhasetwar").

The Examiner finds:

> Thomas (1976) teaches the known use of the Blattoidea BBB for studying the kinetics of exchange of molecules across the insect BBB, and further teaches that this system can be used as a model system to study the vertebrate BBB. Poss et al. provides clear suggestion and motivation for using an insect BBB to study the movement of nanoparticles across the blood brain barrier. Labhasetwar et al. (US7332159B2) describes modifications of the nanoparticle formulation to enhance transport of nanoparticles across the blood brain barrier. (See col. 5, last ¶). Moreover, Stork et al. teaches that the insect BBB, e.g. the Drosophila BBB, is homologous to the mammalian BBB. Stork et al. also teaches that the insect BBB is useful in identifying agents which are capable of crossing the BBB, see Figure 2 and page 594. Furthermore, Mayer et al. states that "[o]n a cellular level, ***the vertebrate and insect BBBs*** share many common features."

(Ans. 6). The Examiner concludes the ordinary artisan "seeking to assess the movement of nanoparticles across the vertebrate BBB . . . would have had a reasonable expectation that the use of insect BBB models from the Blattoidea family, and *Drosophila*, would provide an accurate prediction regarding the movement of nanoparticles across the vertebrate BBB" (Ans. 7).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the prior art renders the claims obvious?

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[5] Stork et al., *Organization and Function of the Blood-Brain Barrier in Drosophila*, 28 J. Neuroscience 587–597 (2008) ("Stork").
[6] Mayer et al., *Evolutionary Conservation of Vertebrate Blood-Brain Barrier Chemoprotective Mechanisms in Drosophila*, 29 J. Neuroscience 3538–3550 (2009) ("Mayer").

Findings of Fact

1. Labhasetwar teaches "injection of . . . [a] nanoparticle formulation via the carotid artery or jugular vein. Using this protocol, it has now been shown that the nanoparticles can cross the blood brain barrier" (Labhasetwar 3:47–50).

2. Labhasetwar teaches administering a "suspension of nanoparticles . . . either via the intracarotid, intrajugular vein, or intravenous route" to rats, incubating the rats for "[o]ne hour after nanoparticle administration . . . and the brains collected for quantitative analysis of nanoparticle uptake" (Labhasetwar 8:53–61).

3. Labhasetwar teaches "the dye concentration in the sample was determined using high performance liquid chromatography (HPLC). A standard plot using nanoparticles was prepared using identical conditions to determine the amount of nanoparticles localized in the brain" (Labhasetwar 9:2–6).

4. Poss teaches a method that

> includes the steps of: (a) administering to a subject an optical imaging probe of the present invention; (b) allowing time for the optical imaging probe to reach the target tissue and, preferably, but not necessary, for molecules in the target tissue to metabolize the probe; (c) illuminating the target tissue with light of a wavelength absorbable by the optical imaging probe; and (d) detecting the optical signal emitted by the optical imaging probe.

(Poss ¶ 32).

5. Poss teaches the test "subject may be a mammal, including a human. The subject may also be non-mammalian, (i.e., C. *elegans, drosophila,* etc.)" (Poss ¶ 33).

6. Poss teaches the "probes of the present invention may be also be constructed using . . . iron oxide nanoparticles" (Poss ¶ 93).

7. Poss teaches "preferred brain imaging agents of the present invention also have blood brain barrier permeability" (Poss ¶ 58).

8. Stork teaches

> different glial cells [in *Drosophila*] . . . comprise the functional blood-brain barrier. The integrity of this barrier can be measured after injection of labeled dextran molecules into the hemolymph . . . the use of differently sized dextran allows addressing a possible size selectivity of the barrier. To determine the kinetics of dextran uptake we used a Zeiss 5 Live LSM . . . . This allowed us to directly follow and quantify the dextran uptake in living embryos.

(Stork 590, col. 1–2).

9. Stork teaches:

> In *Drosophila* two Claudin-like proteins have been described to be required for formation of normal epithelial barrier formation . . . . Here, we show that both Sinuous and Megatrachea are also needed for the establishment of normal blood-brain barrier formation. Similarly, it was shown previously that mammalian *claudin5* is a major component of tight junctions of brain endothelial cells. *claudin5* mutant mice show no structural or ultrastructural deficits, but have an impaired blood-brain barrier.

(Stork 594, col. 1–2).

10. Mayer teaches "on a cellular level, the vertebrate and insect BBBs share many common features. . . . The *Dm* proteins that make up the

pleated septate junctions [in *Drosophila*] are nearly identical to the vertebrate proteins that compose the tight junctions" (Mayer 3538, col. 2).

11. Mayer teaches:

> BBB-specific genes and processes found in model organisms, particularly *Drosophila*, could lead to novel insights into the organization and cellular separation of the multiple protective BBB physiologies. These considerations, we believe, make our model system remarkably useful in terms of understanding how ancient and resilient organisms, such as the fruit fly, protect their CNS. Last, this approach may promote the identification of common, conserved regulatory pathways that contribute to chemical protection biology and BBB physiology across species.

(Mayer 3549, col. 2).

12. Thomas teaches, in studies on cockroaches, "that the insect central nervous system is highly permeant to the alcohols, as expected from their comparatively high liposolubility. They are also broadly in agreement with those obtained on the mammalian central nervous system, which also possesses a blood-brain barrier" (Thomas 9).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Wrigley found a "strong case of obviousness based on the prior art references of record. [The claim] recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another." *Wm.*

Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356, 1364 (Fed. Cir. 2012).

Analysis

We adopt the Examiner's findings regarding the scope and content of the prior art (Ans. 2–7; FF 1–12) and agree that the claimed method would have been obvious over the teachings of Thomas, Poss, Labhasetwar, Stork, and Mayer.

Appellants contend "[n]one of the cited references teach or suggest using insects from the orders Acridoidea (e.g., locusts) or Blattodea (e.g., cockroaches) **for determining whether a nanoparticle is transported across the blood brain barrier (BBB)**" (App. Br. 9) (emphasis original).

We find this argument unpersuasive because the Examiner's rejection is based on obviousness, not anticipation. Labhasetwar teaches a process of determining whether, and how much, nanoparticle is transported across the blood-brain barrier that differs from claim 1 solely in studying rats rather than insects (FF 1–3). Similarly, Poss teaches a process for determining whether an imaging probe reaches a desired target tissue in a subject (FF 4) where the subjects include insects like *Drosophila* (FF 5), the imaging probe may be nanoparticles (FF 6), and the imaging agent may require passing the blood-brain barrier (FF 7). Stork teaches a process for determining whether a compound passes the blood-brain barrier in *Drosophila* that involves administering the compound to the insect, incubating the insect, and visualizing the compound in the insect's brain (FF 8–9). Mayer teaches that "vertebrate and insect BBBS share many common features" (FF 10) and suggests the use of insect model systems for "identification of common,

conserved regulatory pathways that contribute to chemical protection biology and BBB physiology across species" (FF 11). Thomas teaches results on cockroach blood-brain barriers that were "in agreement with those obtained on the mammalian central nervous system" (FF 12).

Therefore, we agree with the Examiner that the ordinary artisan, informed by Labhasetwar and Poss of processes for analyzing nanoparticle delivery to the blood-brain barrier, informed by Stork and Mayer of commonalities between insect and mammalian blood-brain barriers and by Mayer's teaching of insects as a model system (FF 11), would have reasonably selected known insect equivalents for testing of blood-brain barrier accessibility to nanoparticles, including the cockroach system demonstrated by Thomas as a known equivalent insect system that shares features with the mammalian system (FF 12) because "all that was required to obtain that combination was to substitute one well-known . . . agent for another." *Wrigley*, 683 F.3d at 1364.

Appellants separately argue each of the references, contending that "Thomas fails to teach the limitations of the intact BBB as alleged by the Office"; that there "is no disclosure in Poss, implicit or explicit, that describes the use of Drosophila as a model for determining blood brain barrier (BBB) penetration of nanoparticles in mammals"; that "Labhasetwar, similar to Poss, does not disclose or suggest that Drosophila, much less any insects from the orders recited in claim 1 are useful as an intermediate model for determining BBB penetration of nanoparticles in mammals"; that "Stork does not disclose or suggest anything about the BBB permeability of nanoparticles in Drosophila"; and that "Mayer simply describes similarities

between the molecular architecture of Drosophila BBB with that of human BBB" (App. Br. 9–10).

We do not find these arguments persuasive because they fail to address the combination of teachings, rather than the teachings of any single reference alone. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). A reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *Id.*

Appellants contend, regarding claims 5, 9, and 10, that "the Office Action fails to point to any teaching in the cited references wherein measuring the concentration of the nanoparticle is performed by homogenizing the dissected brains and analyzing the concentration of the nanoparticle in the homogenate by liquid chromatography" (App. Br. 10). Appellants further contend "the Office must provide a reason why one of ordinary skill in the art would perform the method steps in claims 5 and 9–10, along with the limitations recited in the claims they depend therefrom" (*Id.*).

We do not find this argument persuasive because Labhasetwar teaches the amount of a component in dissected brain samples (FF 2) "was determined using high performance liquid chromatography (HPLC). A standard plot using nanoparticles was prepared using identical conditions to determine the amount of nanoparticles localized in the brain" (FF 3). As the Examiner reasons, "[a]lthough . . . [Labhasetwar's] method was employed using a rat model of the BBB, it is clear that this method of quantifying the

level of nanoparticle uptake into the brain is not novel and can be applied in other systems with an intact BBB, including insect models of the vertebrate BBB" (Ans. 10). That is, Labhasetwar's method of measuring nanoparticles in rat brains (FF 3) may reasonably be applied to other known model systems for the blood-brain barrier including cockroaches (FF 12). Thus, application of the method in the claimed insect models is obvious.

Appellants contend "[a]t the very most, Thomas teaches tissue extracts from a neural cord, not a BBB. For at least these reasons, Thomas teaches away from the claimed invention" (App. Br. 12). Appellants contend that "[s]imilar to Thomas, Poss also teaches away from the Applicants' claimed invention. Poss fails to teach or suggest incubating an optical imaging probe on an intact insect. What's more, Poss does not teach or suggest the use of an intact BBB" (App. Br. 12).

We find the teaching away arguments unpersuasive. A teaching away requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) ("The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed"). Appellants do not identify, and we do not find, any teaching in any of the cited prior art which teaches criticizes, discredits, or discourages the use of cockroach blood-brain barriers as a model system in the nanoparticle screening process of Labhasetwar (FF 1–3). Indeed, in contrast, Poss teaches insects may be screened in such a system (FF 4–5), Mayer teaches insects can serve as model systems for analysis of the blood-

brain barrier (FF 11) and Thomas teaches that cockroach and mammalian blood-brain barriers share common features (FF 12). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971).

Appellants contend:

> Merely because one type of insect (Drosophila) tissue can be used to model aspects of the BBB does not make obvious doing the same in another type of insect. Moreover, the use of Drosophila tissue would not lead one of ordinary skill in the art to another type of insect, in addition to incubation of a nanoparticle on an intact insect. One of ordinary skill in the art would not have a reasonable expectation of success in modeling the BBB in Acridoidea or Blattodea based on the teachings of the cited references, which teach using Drosophila tissue for this purpose.

(App. Br. 14).

We are not persuaded. We agree with the Examiner that there would have been a reasonable expectation of success because

> it was known at the time of the instant invention that the BBB of insects is similar to that observed in mammalian/vertebrate systems. See Mayer et al., which teaches that: "[H]owever, on a cellular level, the vertebrate and insect BBBs share many common features." See page 3538, 2nd paragraph. Furthermore, Stork et al. (see page 591, last paragraph) taught the use of an insect model to assay for the movement of nanoparticles across the BBB. Stork et al. also teaches that regulation and differentiation of the insect nervous system appears to be conserved, see page 587.

(Ans. 11). Indeed, all of the evidence of record (FF 5, 9–11), as opposed to attorney argument, suggests that cockroach and *Drosophila* blood-brain

barriers are similar to those of mammals such as rats, and that there are "common, conserved regulatory pathways that contribute to chemical protection biology and BBB physiology across species" (FF 11). *See In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) ("Attorney's argument in a brief cannot take the place of evidence.").

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the prior art renders the claims obvious.

SUMMARY

In summary, we affirm the rejection of claims 1, 5, 9, and 10 under 35 U.S.C. § 103(a) as obvious over Thomas, Poss, Labhesetwar, Stork, and Mayer. Claims 3, 4, 6, 7, 11, and 12 that were not separately argued fall with claim 1.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED